### Roundup 2.0: Enabling Comparative Genomics for over 1800 Genomes

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Roundup 2.0: enabling comparative genomics for over 1800 genomes

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ABSTRACT

Summary: Roundup is an online database of gene orthologs for over 1800 genomes, including 226 Eukaryota, 1447 Bacteria, 113 Archaea and 21 Viruses. Orthologs are inferred using the Reciprocal Smallest Distance algorithm. Users may query Roundup for single-linkage clusters of orthologous genes based on any group of genomes. Annotated query results may be viewed in a variety of ways including as clusters of orthologs and as phylogenetic profiles. Genomic results may be downloaded in formats suitable for functional as well as phylogenetic analysis, including the recent OrthoXML standard. In addition, gene IDs can be retrieved using FASTA sequence search. All source code and orthologs are freely available.

Availability: http://roundup.hms.harvard.edu

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1 INTRODUCTION

Orthologs are genes from different organisms that descend from a single ancestral gene in the most recent common ancestor (Fitch, 1970). In comparative genomics, they are used to infer the function of novel genes from the function of well-studied ones, to construct phylogenies and explore the evolution of genes and species, and to study sequence conservation and change. They are also valuable in analyzing gene networks, studying gene gain and loss, and finding genes in model organisms that correspond to human disease genes (Altenhoff and Dessimoz, 2009; Gabaldon et al., 2009; Kristensen et al., 2011).

Advances in high-throughput genomic sequencing have made it possible to produce many datasets in a relatively short time period. For example, from 2006 to 2011, the number of complete proteomes listed in UniProtKB (Magrane and Consortium, 2011), a repository of annotated protein sequences, has increased from around 300 to over 2500. To overcome the engineering challenges of computing and publishing orthologs for such a large number of genomes, we redesigned the comparative genomics tool, Roundup (DeLuca et al., 2006), to scale with the rate of genome sequencing and to enable increasingly more sophisticated comparative genomics analyses. Roundup 2.0 contains orthology data for over 1800 genomes, providing one of the largest diversities among similar orthology databases (Chen et al., 2006; Datta et al., 2009; Huerta-Cepas et al., 2011; Kristensen et al., 2011; Li et al., 2006; Linard et al., 2011; Ostlund et al., 2010; Rouard et al., 2011; Schneider et al., 2007; Tatusov et al., 2003). Roundup compares well to other major databases, with recent studies showing similar ortholog composition for model organisms (Altenhoff and Dessimoz, 2009; Chen et al., 2007). The data in Roundup include clusters of orthologs for a wide range of sequence conservation, allowing searches for distant orthologs, and also phylogenetic profiles that enable functional investigation, phylogenetic analysis and prediction of network organization (Cui et al., 2011).

2 ALGORITHMS

We used the reciprocal smallest distance (RSD) (Wall et al., 2003) algorithm to infer orthologs. RSD improves the sensitivity of reciprocal best blast hits by considering global alignment and maximum likelihood evolutionary distance between sequences. As a pairwise orthology algorithm, RSD scales quadratically with the number of genomes in Roundup. Altenhoff et al. assessed 10 ortholog inference projects and methods, confirming the reliable performance of RSD over a wide array of genomes from the tree of life (Altenhoff and Dessimoz, 2009).

For Roundup 2.0, we changed RSD to improve its speed, stability and ortholog inference. We replaced WU-BLAST (W.Gish, personal communication) with NCBI BLAST (Altschul et al., 1990). Also, we replaced ChustalW (Thompson et al., 1994) with Kalins (Lassmann and Sonnhammer, 2005). Kalins is faster than ChustalW and produces better alignments for more distantly related sequences. This change resulted in 9% closer maximum likelihood distances between orthologs computed using PAML 4.0 (Yang, 2007), and 0.3% more orthologs on average. Since the Roundup database stores orthology for 12 combinations of divergence and E-value thresholds, RSD was modified to compute orthologs for any number of parameter combinations as quickly as for one parameter combination. This change should be of interest to researchers investigating the effect of different parameter settings and degree of global sequence similarity on ortholog inference. With the addition of other caching and file I/O changes, RSD is over six times faster than the previous version in our performance tests.

In addition to housing the orthologs inferred by RSD, Roundup builds clusters of orthologous genes, i.e. ortholog groups, using deterministic single-linkage clustering. It partitions a graph into connected subgraphs by creating a cluster for every gene and then
merging two clusters if a gene in one of the clusters is orthologous to a gene in the other one. The result is that every gene in a group is orthologous to at least one other gene in the group and to no genes in any other groups. In contrast to other orthology databases (Chen et al., 2006; Schneider et al., 2007; Tatusov et al., 2003), Roundup orthologous groups are built on the fly using genomes selected by the user. This allows users to include exactly their genomes of interest and to explore the effects of including different genomes on the grouping of orthologs.

3 GENOMES AND ORTHOLOGS

The 1807 genomes in Roundup 2.0 are from UniProtKB (Magrane Orthologous groups are built on the fly using genomes selected by the Browse available in Roundup. The genomes and orthologs are updated 2–4 threshold settings. As a result, there are over 11 billion orthologs across 12 parameter combinations selected to allow researchers access to results for a broad range of divergence and computing cluster. Roundup used a fault-tolerant computational years to compute the orthologs took several weeks on our research Consortium, 2011), including 226 Eukaryota, 1447 Bacteria, 113 sequences for genes in orthologous groups are also provided for and Consortium,U. (2011) UniProt Knowledgebase: a hub of integrated summaries by GO Terms and by Gene Clusters. The orthologous protein names and GO Process terms provided by UniProtKB and Gene Ontology (Ashburner,M. et al., 2006; Schneider,A. et al., 2007; Tatusov,R. L. et al., 2003; Chen,F. et al., 2007) are provided to support interoperability with other orthologs in OrthoXML and text formats; and code for RSD and Orthology databases and the quest for orthologs (Gabaldon et al., 2008). Query results are cached for up to 30 days and may be retrieved by using the initial URL.

To support research and replication, we make available for downloading from the website: FASTA sequences for genomes; orthologs in OrthoXML and text formats; and code for RSD and Roundup. Orthologs are also available through an HTTP-based API. Roundup 2.0 is an important step forward towards keeping pace with the rate of genome sequencing. The features and flexibility of Roundup 2.0, coupled with the wide coverage of genomes, enables increasingly large-scale comparative genomics analyses that address key questions in phylogeny, genome evolution and systems biology.

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Conflict of Interest: none declared.

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